## REMARKS

Claims 1 and 3-29, as amended, are pending in this application for the Examiner's review and consideration. Claim 1 has been amended to incorporate the subject matter of claim 2, which has been canceled. Support for this amendment is also found in the specification, e.g., paragraphs [0012] and [0016] of the published application. Claims 1 and 16 have been further amended to recite generating a plurality of micro-channels, and claims 9 and 23 have been amended to correct antecedent basis, support for which is found in the specification, e.g., paragraph [0029] of the published application. Claim 1 has also been amended to correct a typographical error, while claim 16 has been amended to make it clear that the microchannels are formed after administration of the composition. Claims 30-36 have been canceled without prejudice. As no new matter has been introduced by any one of these changes, they should all be entered at this time.

Priority

The Examiner indicates that applicant has not filed a certified copy of the foreign priority application as required by 35 U.S.C. 119 (b). Applicants respectfully submit that a certified copy of the priority document Israel Patent Application No. IL 160033 has been filed and was received by the International Bureau on February 21, 2005, as evidenced by the enclosed copy of this priority document.

Claim Objection

Claim 1 has been objected to for a misspelling. In response, the misspelled word "channel" has been corrected. Therefore, the objection has been overcome and should be withdrawn.

Claim Rejections – 35 USC § 102

Claims 1-7, 9, 10, 15-21, 23, 24, 29-31 and 36 have been rejected under 35 U.S.C. 102(b) as allegedly being anticipated by U.S. Patent Application No. 2003/0208152 to Avrahami et al. (referred herein after as "Avrahami"). The Examiner indicates that regarding claims 1 and 16, Avrahami discloses a method of delivering an oligonucleotide or polynucleotide via the following: generating at least one micro-channel in the skin of a subject (Paragraph 17) and

applying to the skin a pharmaceutical composition of an acceptable carrier (conductive substance – Paragraph 32) with an active ingredient (Paragraph 33) of an oligonucleotide or polynucleotide (Paragraph 255). The Examiner further indicates that regarding claim 2, Avrahami uses the plural when discussing generating channels (Paragraph 167) and specifically discusses design parameters for an electrode array (Paragraph 175).

Applicant respectfully disagrees with the Examiner's rejections. Avrahami discloses devices and methods for enhancing transdermal movement of a substance. The methods comprise a step of generating at least one micro-channel in the stratum corneum to enable or augment transdermal movement of the substance (see. e.g., paragraphs [0017], [0036], [0037], [0112], [0137], [0167] of Avrahami). The substance according to Avrahami is actively or passively delivered to the skin following ablation of the skin (see. e.g., paragraphs [0037], [0137], and [0167] of Avrahami). Devices and methods for actively delivering the substance are disclosed: a pressure generating unit used to propel the active substance by gas, an ultrasonic transducer, or iontophoresis (see, e.g., paragraph [0042] of Avrahami). Thus, Avrahami discloses devices and methods for forming micro-channels by ablating the stratum corneum in order to increase skin conductance to the passage of molecules therethrough (see, e.g., paragraph [0020] of Avrahami), namely generating micro-channels before application of an active substance. Avrahami neither discloses nor suggests a method which comprises generating micro-channels after application of an active substance.

In contrast, the present invention discloses that generating micro-channels in an area of the skin before application to that area of the skin of a pharmaceutical composition comprising an oligonucleotide or polynucleotide and also after such application enhances the transdermal delivery of the oligonucleotide or polynucleotide compared to the delivery obtained by generating micro-channels only before application of the pharmaceutical composition (see, e.g., paragraph [0012] of the published application). Moreover, transdermal delivery of an oligonucleotide or polynucleotide can be achieved even if the micro-channels are generated only after application of the pharmaceutical composition on an area of the skin. Accordingly, claim 1 has been amended to include the subject matter of claim 2, i.e., claim 1 now recites a method for intradermal or transdermal delivery of an oligonucleotide or polynucleotide comprising: (a) generating a first plurality of micro-channels in an area of the skin of a subject; (b) applying to the area of the skin a pharmaceutical composition comprising an oligonucleotide or

polynucleotide and a pharmaceutically acceptable carrier; and (c) generating a second plurality of micro-channels in said area of the skin. Claim 16 has been amended to make it clear that the microchannels are formed after applying the composition. Thus, neither claim 1 nor claim 16, as amended, can be anticipated by Avrahami. Therefore, claims 3-7, 9, 10, and 15 which depend from claim 1 and include further recitations thereto, and claims 17-21, 23, 24, and 29 which depend from claim 16 and include further recitations thereto are not anticipated by Avrahami. Also, claims 30-36 have been canceled. Accordingly, the anticipation rejections of claims 1 and 16, and the claims dependent therefrom should be withdrawn.

Claim Rejections – 35 USC § 103

Claims 8 and 22 have been rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over Avrahami as applied to claim 1, and further in view of U.S. Patent No. 6,429,200 to Monahan et al. (referred herein after as "Monahan"). The Examiner indicates that while Avrahami substantially discloses the apparatus as claimed, it does not disclose additives to the active agent such as lipids, polycations or nuclease inhibitors. The Examiner indicates that Monahan discloses adding polycations to polynucleotides and reverse micelles in order to compact the polynucleotides. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the delivery device/method of Avrahami to utilize polycations and reverse micelles as taught by Monahan to compact the polynucleotides for gene delivery purposes.

As explained above, Avrahami does not disclose or suggests a method for intradermal or transdermal delivery of an oligonucleotide or polynucleotide by generating micro-channels in the skin after application of a composition that contains an oligonucleotide or polynucleotide. Monahan does not remedy the deficiencies of Avrahami.

Monahan discloses a complex for delivery to a cell comprising: the complex formed by the process of inserting a nucleic acid into a reverse micelle (see, e.g., col. 5, lines 55-63 of Monahan). According to Monahan, compounds can be added to the nucleic acid/micelle mixture. Among the compounds, polymers such as polyions (polycations, polyamines, and polyanions) are listed (see, e.g., col. 5, line 67 through col. 6, line 6 of Monahan). Monahan does not disclose or suggests the last method step recited in claims 1 and 16. Also, as noted above, Avrahami does not disclose or teach that step. Thus, even if one combines Avrahami and

Monahan, he would not obtain the methods of intradermal or transdermal delivery of oligonucleotide or polynuleotide as recited in claims 8 and 22 which adds further features to claims 1 and 16, respectively. Therefore the obviousness rejection of these claims has been overcome and should be withdrawn.

Claims 10-14, 24-28 and 31-35 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Avrahami. The Examiner indicates that regarding claims 10, 24, and 31, it would have been obvious to one of ordinary skill in the art at the time the invention was made to generate micro-channels of uniform shape and dimension so as to homogenously deliver the active agent which is notoriously well known within the art as being more desirable than uneven delivery absent any other considerations. Regarding claims 11-14, 25-28, and 32-35, the Examiner indicates that it would have been obvious matter of design choice to a person of ordinary skill in the art to determine and assign diameters and lengths to the electrodes because Applicant has not disclosed that such a limitation provides an unexpected advantage.

As explained herein, Avrahami does not disclose or suggest the methods recited in claim 1 as amended and in claim 16. Therefore, claims 1 and 16 are patentable over Avrahami. As claims 11-14 and 25-28 depend from claims 1 and 16, respectively, and include further recitations thereto, these claims are patentable over Avrahami, and therefore the rejection of these claims should be withdrawn. As claims 30-36 have been canceled, the rejection of claims 31-35 should also be withdrawn.

Claims 15, 29, and 36 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Avrahami as applied to claim 9, and further in view of U.S. Patent Application No. 2005/0287217 (referred herein after as "Levin") and U.S. Patent No. 6,148,232 (referred herein after as "Avrahami '232").

As indicated above, Avrahami does not disclose or suggest the methods recited in claim 1 as amended and in claim 16. Levin and Avrahami '232 do not remedy the deficiencies of Avrahami.

Avrahami '232 discloses a device for ablating the stratum corneum epidermidis of a subject, including a plurality of electrodes, which are applied to the subject's skin at respective points. A power source applies electrical energy between two or more of the plurality of electrodes, in order to cause ablation of the stratum corneum primarily in an area intermediate the respective points (see, e.g., abstract of Avrahami '232). According to Avrahami '232, micro-

channels are generated in the stratum corneum to enable or augment transdermal movement of a substance (see, e.g., col. 2, lines 59-67 of Avrahami '232), namely micro-channels are generated before application of a drug (see, e.g., col. 6, lines 29-33 of Avrahami '232).

Levin discloses a method for intradermal or transdermal delivery of water soluble, poorly soluble, or insoluble cosmetic agents comprising: (i) generating at least one micro-channel in a region of skin of a subject suffering from a skin condition; and (ii) topically applying a cosmetic or dermatological composition comprising a dermatologically effective amount of at least one water-soluble, poorly water-soluble, or water-insoluble cosmetic agent and a cosmetically or dermatologically acceptable carrier to the region of the skin in which the micro-channels are present so as to improve the skin condition of said subject (see, e.g., paragraphs [0030] to [0032] of Levin). Thus, according to Levin, the micro-channels must be generated before application of a dermatological or cosmetic composition. Thus, even if one of ordinary skill in the art combines Avrahami, Levin, and Avrahami '232, he would not obtain the method claims as recited in claims 1 and 16 as amended, and therefore claims 1 and 16 are patentable over Avrahami in view of Levin and Avrahami '232. Applicants respectfully submit that teachings of making microchannels prior to administration of a composition do not render unpatentable claims directed to generating microchannels after application of the composition. Also, as claims 15 and 29 depend from claims 1 and 16, respectively, and include further limitations thereto, claims 15 and 29 are also patentable over Avrahami in view of Levin and Avrahami '232. Claim 36 has been canceled. Accordingly, the rejection of these claims should be withdrawn.

In view of the above, it is respectfully submitted that all current rejections have been overcome and should be withdrawn. Accordingly, the entire application is believed to be in condition for allowance, early notice of which would be appreciated. Should the Examiner not

agree, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of this application.

Respectfully submitted,

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